NOTES TO FILE

8/21/03

Carbaryl Post-IRED Meeting with Bayer on a Pharmacokinetics Study to Refine Risk Estimates. On August 21, 2003, representatives from Bayer CropScience and their consultant, InfoScientific, met with staff from HED, SRRD and EPA's Office of Research and Development (ORD) to discuss physiologically based pharmacokinetics (PBPK) modeling work currently underway in ORD for the carbamates. Bayer, a technical registrant for carbaryl, is interested in using PBPK data to refine residential risk concerns identified by the Agency for lawn liquid broadcast uses of carbaryl. In the carbaryl IRED, signed on June 30, 2003, the technical registrants for carbaryl agreed to remove from their labels certain lawn liquid broadcast uses due to EPA's risk concerns. They also provided EPA with a voluntary cancellation letter post-dated for June 30, 2004. The IRED notes, however, that Bayer CropScience is working on PKPB data to further refine these risks of concern. Bayer is attempting to complete work on this study by April 2004, so that EPA can review this new data before June 2004, and possibly reconsider cancellation of the lawn liquid broadcast use. Bayer has also requested a follow-up meeting with EPA to discuss the data and the protocols that Bayer will need to develop for an acceptable PBPK study (Tony Britten, 308-8179).

2-4-04

Carbaryl Team Meets with Bayer CropScience About Use of PBPK Data for EPA's Upcoming Decision on Residential Turf Use (liquid broadcast applications).

On Wednesday, Bayer briefed an expanded carbaryl team, including representatives from ORD, on progress toward submitting physiologically-based pharmacokinetic (PBPK) data to refine Agency risk estimates for carbaryl's liquid broadcast lawn use; EPA estimated toddler risks of concern for postapplication exposures (MOE = 5). The carbaryl IRED states that EPA will decide the fate of the liquid broadcast lawn use by June 30, 2004. Part of Wednesday's meeting was to determine what data Agency risk managers will likely have by that date. On-going Bayer lab studies are taking rat tissue samples to establish carbaryl concentrations and cholinesterase inhibition following dosing at the NOAEL and LOAEL, looking particularly for peak concentrations/inhibition and the rate of decline. Bayer has proposed a further study to assess tissue concentrations at much lower doses, consistent with Agency scenarios for the most exposed toddler. PBPK data for carbaryl is also relevant to OPP and ORD for potential modeling of risks for the carbamate cumulative assessment.

Other notes: Bayer Presents Carbaryl PBPK Data and Modeling Approaches. A meeting was held on February 4th with representatives from Bayer Crop Protection to discuss their ongoing efforts to refine risk estimates for carbaryl use on lawns. The approach presented by Bayer is based on the use of PBPK data and modeling. Three major issues were discussed including (1) the status of their ongoing studies which are intended to quantify the pharmacokinetics of carbaryl dosed orally, dermally, and by IV, cholinesterase inhibition

measurements are also included; (2) how these data will be used for risk assessment - at this point their proposal is to use the data and not rely heavily on additional PBPK modeling (e.g., ERDEM from ORD/NERL); and (3) the completion of another study at doses intended to simulate those calculated for children in the risk assessment. Representatives from SRRD attended as well as ORD staff from NERL and NHERL who have also been involved in this process..

5/19/04

Beekeepers Meet with OPP; Issues include Bee Advisory Label Language for Carbaryl
On May 19, representatives from several national bee organizations and two individual beekeepers from Minnesota, as well as Jennifer Sass from NRDC, met with OPP to discuss several issues of importance to beekeepers, including: (1) beekeeper needs for pesticide registrations important for controlling pests that affect bees, such as verola mite; (2) deleterious effects on bees from crop uses of neonicotinics, such as imidichloprid; and (3) bee advisory labeling issues, both generally, and also specifically related to effects on bees from carbaryl applied to poplar plantations in Minnesota. On this last issue, beekeepers asked OPP for a written interpretation of commonly used bee advisory labeling. OPP stated generally the difficulty in supplying a generic label interpretation that meets the needs of all parties (beekeepers and applicators) in all places, but stated a desire to continue dialogue. Region 5 also participated in the call.

5/28/04

Yesterday afternoon, David Herr, Jeff Dawson, Kit Farwell, Anna Lowit and Tony Britten talked via teleconference with Bayer (Curt Lunchick, Danielle LaRochelle, Ian Kennedy, and Jim Campbell) about a possible descrepancy between the results of recent pharmacokinetic data Bayer submitted to refine turf risks for toddlers, and some preliminary method validation work that ORD/NHERL has done with carbaryl related to the carbamate cumulative. The preliminary NHERL data suggest a peak in carbaryl detections in plasma following oral dosing. The Bayer data does not show a peak. The respective analytical methods, however, differ considerably. ORD/NHERL and Bayer plan to meet in RTP on Wednesday, June 1, to compare their respective analytical methods and dosing regimines to determine if there is a problematic inconsistency in test results. The outcome of these discussions between Bayer and ORD might impact how Bayer's pharmacokinetic data could be used to calculate a refined MOE for toddler postapplication exposures to toddlers from whole lawn liquid treatments of carbaryl.

6/28/04
Carbaryl PBPK Turf Use Meeting between EPA and Bayer
On June 11, Bayer submitted a paper to EPA titled: "Application of Carbaryl Pharmacokinetic Data in the Estimation of Potential Post-Application Health Risks Associated with Broadcast Lawn Care Products: Interim Draft Report." On June 28, 2004, EPA met with Bayer CropScience about their use of PBPK data to refine EPA's risk estimates for toddlers exposed to residential turf following whole lawn treatment with carbaryl liquid. The purpose of the meeting

was for Bayer to present a synopsis of their report (a powerpoint presentation is attached to this Note) and to answer any questions raised by EPA's Carbaryl Team, including OPP and ORD scientists, as well as risk managers. No decisions were made at the meeting. SRRD needs a formal review of the Bayer submission from Agency scientists before making a decision about broadcast liquid application of carbaryl to residential turf. Bayer CropScience presented slides that were essentially excerpts from the full report, which would be FIFRA reregistration data subject to 10G signature. [Must get Bayer's permission to post this document].

A list of attendees from the June 28 meeting follows:
EPA attendees. SRRD: Michael Goodis, Tony Britten, Dr. Mark Seaton. HED: Jeff Dawson, Dr. Anna Lowit, Jeff Evans. ORD: Dr. David Herr, Dr. Curt Dary, Dave Powers, Dr. Miles Okino. **Bayer attendees:** Joe Hudson, Dr. Abe Tobia, Curt Lunchick, Dr. Mike Krolski, Dr. Jim Campbell, Karen Shearer, Norma Pangilinan, and Joe Conti. **Other attendees:**
Rory Conolly, CIIT Centers for Health Research (working with Bayer on PBPK modeling)